PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7:		(11) International Publication Number: WO 00/24893
C07K 14/505, 38/18, A61P 7/06, C12N 5/10, 15/12	A3	(43) International Publication Date: 4 May 2000 (04.05.00)
 (21) International Application Number: PCT/US (22) International Filing Date: 18 October 1999 ((30) Priority Data: 09/178,292 23 October 1998 (23.10.98) (71) Applicant: AMGEN INC. [US/US]; One Amgen Cen Thousand Oaks, CA 91320–1799 (US). (72) Inventors: EGRIE, Joan, C.; 561 Dos Vientos Drive, Park, CA 91320 (US). ELLIOTT, Steven, G.; 104 Crest Avenue, Newbury Park, CA 91320 (US). Jeffrey, K.; 1244 Calle Aurora, Camarillo, CA 93 (74) Agents: ODRE, Steven, M. et al.; Amgen, Inc., Or Center Drive, Thousand Oaks, CA 91320–1799 (Newbu 10 Gold BROW 010 (Usine Amg	BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report.

(54) Title: METHODS AND COMPOSITIONS FOR THE PREVENTION AND TREATMENT OF ANEMIA

(57) Abstract

Methods for increasing and maintaining hematocrit in a mammal comprising administering a hyperglycosylated analog of erythropoietin are disclosed. An analog may be administered less frequently than an equivalent molar amount of recombinant human erythropoietin to obtain a comparable target hematocrit and treat anemia. Alternatively, a lower molar amount of a hyperglycosylated analog may be administered to obtain a comparable target hematocrit and treat anemia. Also disclosed are new hyperglycosylated erythopoietin analogs, methods of production of the analogs, and compositions comprising the analogs.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

ì	AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
	AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
Ì	АT	Austria	FR	France	LU	Luxembourg	SN	Senegal
1	AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
1	ΑZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
	BA	Bosnia and Herzegovina	GE	Georgia '	MD	Republic of Moldova	TG	Togo
	BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
	BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Terkmenistan
	BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
	BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
	Bj	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
ŀ	BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
Ì	BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
ľ	CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
	CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
	CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
ł	CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
	CI	Côte d'Ivoire	KP	Democratic People's	NZ.	New Zealand		
	CM	Cameroon		Republic of Korea	PL .	Poland		
	CN	China	KR	Republic of Korea	PТ	Portugal		
	Cυ	Cuba .	KZ	Kazakstan	RO	Romania		
Į	CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
1	DE	Germany	LI	Liechtenstein	SD	Sudan		
I	DK	Denmark	LK	Sri Lanka	SE	Sweden		
I	EE	Estonia	LR	Liberia	SG	Singapore		
ı								

Inter anal Application No
PCT/US 99/24435 -=

A. CLASSIF IPC 7	CO7K14/505	MATTER A61K38/18	A61P7/06	C12N5/10	C12N15/12 -
According to	International Patent Clas	saification (IPC) or to bot	h national classificat	ion and IPC	
B. FIELDS					
	currentation searched (c	lassification system follo	wed by classification	n symbols)	
IPC 7	CO7K A61K				
			40 the endered the deci-		
Documentati	on saarched other than r	manum occumenzation	io the exishi that su	ch documents are included in	n the heigs searched
Flectronic or	ata pase consuted dinut	Ine international search	1 (name of Cara Das	e and, where practical, search	n terms used)
-					
C. DOCUME Category	Citation of document to	ith Indication, where ap	consists of the role	Hart presence	Relevant to daim No.
Category	Citation of document, w	an traceator, where ap	Propriete, or the tere	valii passayes	Leiga Stiff in Cismit 140°
χ	WO 95 0546	5 A (AMGEN IN	ic)		23-32
	23 Februar	y 1995 (1995-	02-23)		,
		he applicatio 7,9,17,19,22,			
Α		tables 3,5,6			1-22
			•		
X		7 A (AMGEN IN (1991-05-02)			23–32
	cited in t	he applicatio		•	
	claims 2,	5,9,10			
X	EP 0 267 6	78 A (INTEGRA	TED GENETI	CS INC)	23-32
^	18 May 198	8 (1988-05-18	3)	•	
	page 1, li	ne 9 - line 1	7; claims	1-6	
			_	/	
		•			:
X Furt	her documents are listed	in the continuation of bo	× C.	X Patent family memb	ere are listed in annex.
Special ca	tegories of cited docume	nte :		T* later document published	after the International filing date
	ent defining the general st tered to be of particular re			or priority date and not in cited to understand the p	n conflict with the application but principle or theory underlying the
"E" earlier	document but published o		nai		levance; the claimed invention
	ent which may throw dout			involve an inventive step	ovel or cannot be considered to by when the document is taken alone
citatio	is cited to establish the p n or other special reason	(as specified)		cannot be considered to	levance; the claimed invention involve an inventive step when the
other	ent referring to an oral dis means				vith one or more other such docu- n being obvious to a person skilled
P docum: later t	ent published prior to the han the priority date clain	International filing date to ned		*& document member of the	same patent family
Date of the	actual completion of the	international search		Date of mailing of the int	ternational search report
2	8 April 2000			17/05/2000	
Name and	mailing address of the IS		- 0	Authorized officer	
	NL - 2280 HV Rijev	fice, P.B. 5818 Patentia: vijk 2040, Tx. 31 651 epo ni.	ui 4	-	•
l .	Fave (+31-70) 340	2016		Tevssier.	Б

1

Inte Jonal Application No PCT/US 99/24435

(Continu	ation) DOCUMENTS CONSIDERED TO BE RELEVANT	
ategory °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
1	US 5 541 458 A (HIRST B MARK) 30 July 1996 (1996-07-30) column 6, line 14 - line 22 column 8, line 14 - line 23 claims 5,6,14,15,17-21	1-22, 31-37
\	US 5 716 644 A (BRICKNER AVRAM ET AL) 10 February 1998 (1998-02-10) column 1, line 23 - line 48	1-22, 31-37
A	FIBI M R ET AL: "N- AND O-GLYCOSYLATION MUTEINS OF RECOMBINANT HUMAN ERYTHROPOIETIN SECRETED FROM BHK-21CELLS" BLOOD, vol. 85, no. 5, 1 March 1995 (1995-03-01), pages 1229-1236, XP002053700 page 1235, last paragraph	1-37
A	EGRIE J C ET AL.: "The role of carbohydrate on the biological activity of erythropoietin" GLYCOCONJUGATE JOURNAL, 15 - 20 August 1993, page 263 XP000906829 Abstracts of XIIth International Symposium cited in the application	
A	ELLIOTT STEVE ET AL.: "Structural requirements for addition of O-linked carbohydrate to recombinant erythropoietin." BIOCHEMISTRY, vol. 33, no. 37, 17 September 1994 (1994-09-17), pages 11237-11245, XP000906783	
Ρ,Χ	WO 99 11781 A (FIBI MATHIAS; HERMENTIN PETER (DE); HOECHST MARION ROUSSEL DE GMBH) 11 March 1999 (1999-03-11) claims 1-5,8-10,12,14-19,22	23-31
	·	
		·
j.		

In. . national application No.

INTERNATIONAL SEARCH REPORT

PCT/US 99/24435

Boxi	Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)
This Inte	mational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely: Remark: Although claims 1-22 and 32-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. X	Claims Nos.: 1, 7, 33, 35 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically: see FURTHER INFORMATION sheet PCT/ISA/210
3.	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II	Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)
This Int	emational Searching Authority found multiple inventions in this international application, as follows:
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely pald by the applicant, this international Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remar	k on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 7, 33, 35

Present claims 1 and 33 on one hand and 7 and 35 on the other hand relate to the administration of compounds caracterised (inter alia) by reference to the frequency and dose of administration, respectively. In this context, the wordings "less frequently" and "lower molar amount" with reference to prior art recombinant human EPO were not considered clear within the meaning of Article 6 PCT. Consequently, with respect to claims 2, 8, 34, 36 and line 14, page 4 of the description, the search has been restricted to "two times a week or less" (claim 1) or "one time a week or less" (claim 33) and "total molar amount of less than of 4.5 mug/kg/week or 150 units/kg/week" (claims 7, 35), respectively.

information on patent family members

Intern nal Application No PCT/US 99/24435 =

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9505465 A	23-02-1995	AT 155796 T AU 677097 B AU 7632794 A CN 1105030 A CZ 9500917 A DE 69404401 D DE 69404401 T DK 640619 T EP 0640619 A ES 2105442 T FI 951792 A GR 3024815 T HK 1001589 A HU 72849 A JP 11155584 A JP 2938572 B JP 8506023 T LY 10972 A LV 10972 B NO 951445 A NZ 273134 A SI 640619 T SK 50295 A ZA 9406122 A	15-08-1997 10-04-1997 14-03-1995 12-07-1995 13-03-1996 04-09-1997 19-02-1998 02-02-1998 01-03-1995 16-10-1997 18-05-1995 30-01-1998 28-05-1996 15-06-1999 23-08-1999 02-07-1996 20-12-1995 20-10-1996 16-06-1995 24-11-1997 28-02-1998 09-08-1995 20-03-1995
WO 9105867 A	02-05-1991	AT 146187 T AT 184914 T AU 646822 B AU 6604290 A CA 2027635 A CA 2165694 A CN 1051936 A DE 69029370 D DE 69029370 T DE 69033301 D DE 69033301 T DK 428267 T EP 0428267 A EP 0668351 A ES 2097753 T FI 964648 A GR 3022658 T HK 1006718 A JP 8151398 A JP 2983629 B JP 4502331 T NO 301832 B NZ 235676 A PT 95586 A, B US 5856298 A ZA 9008166 A	15-12-1996 15-10-1999 10-03-1994 16-05-1991 14-04-1991 14-04-1991 05-06-1997 23-01-1997 28-10-1999 20-04-2000 09-06-1997 22-05-1991 23-08-1997 21-11-1996 31-05-1997 12-03-1999 11-06-1996 29-11-1999 23-04-1992 15-12-1997 28-04-1992 30-09-1991 05-01-1999 28-08-1991
EP 0267678 A	18-05-1988	US 4954437 A AU 7842987 A DK 478287 A FI 873897 A JP 63185396 A PT 85699 A,B	04-09-1990 16-03-1989 16-03-1988 16-03-1988 30-07-1988 01-10-1987

information on patent family members

Inter. Mai Application No
PCT/US 99/24435 =

Patent document cited in search repor		Publication date		atent family member(s)	Publication date
US 5541458	A	30-07-1996	EP	0712207 A	15-05-1996
			JP	8256478 A	01-10-1996
US 5716644	Α	10-02-1998	AU	705451 B	20-05-1999
			AU	5972496 A	30-12-1996
			AU	705968 B	03-06-1999
			AU	6034196 A	30-12-1996
			CA	2223583 A	19-12-1996
•			CA	2223834 A	19-12-1996
			CZ	9703908 A	13-05-1998
			EP	0871433 A	21-10-1998
			EP	0831786 A	01-04-1998
		·	. JP	11506764 T	15-06-1999
			NZ	309533 A	30-08-1999
			PL.	323736 A	14-04-1998
			WO	9640073 A	19-12-1996
		•	WO	9640074 A	19-12-1996
			UA	698016 B	22-10-1998
			AU	4275597 A	15-01-1998
			AU	680422 B	31-07-1997
			AU	4630893 A	04-01-1994
			CA	2136434 A	23-12-1993
			EP	0644771 A	29-03-1995
			JP	7507806 T	31-08-1995
			MO	9325221 A	23-12-1993
			US	5674534 A	07-10-1997
WO 9911781	A	11-03-1999	EP	0902085 A	17-03-1999
•			AU	9533798 A	22-03-1999